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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Merton Bernfield and Ofer Reizes

Serial No:	08/965,356	Art Unit:	1632
Filed:	November 6, 1999	Examiner:	A. Baker

For: METHODS AND REAGENTS FOR REGULATING OBESITY

Assistant Commissioner for Patents
Washington, D.C. 20231

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 1,3-6, 10, and 12-15 in the Office Action mailed February 1, 2000 in the above-identified patent application. A Notice of Appeal was filed on June 30, 2000. A check in the amount of $155 for the filing of this Appellants' Brief is also enclosed. A Petition for an Extension of Time for three months, up to and including November 30, 2000, and the appropriate fee for a small entity, are enclosed with this Appeal Brief.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is the assignee, Children's Medical Center Corporation, Boston, MA

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS ON APPEAL

Claims 1, 3, 4, 5, 6, 10, 13, 14 and 15 are pending and on appeal. The text of each claim on appeal, as amended, is set forth in the Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

The claims were last amended by the Amendment maled January 7, 2000 with the request for filing of a continuating prosecution application.

(5) SUMMARY OF THE INVENTION

Lines of transgenic rodents have been developed which preferentially express a syndecan in the regions of the hypothalamus which are known to be important in weight control. (p. 4, l. 25-28) The animals were made using a construct including a cytomegalovirus promoter and the 3' untranslated region, including the polyadenylation site, of the bovine growth hormone gene, as well as cDNA encoding syndecan-1. (p. 4, l. 28-30) The mice express the syndecan-1 transgene in many tissues, with expression in the brain occurring preferentially in their hypothalamus. (p. 4, l. 30-32) The mice are characterized by elevated levels of circulating syndecan-1 ectodomain and exhibit enormous weight gain after reaching sexual maturity. (p. 5, l. 1-2) Transgenic animals in which stop codons have been inserted into the construct so that the syndecan is not

expressed do not exhibit the same enormous weight gain. (p. 5, l. 2-5) The animals have a relatively normal distribution of fat, are completely healthy and heterozygotes reproduce, and show other indicators associated with obesity in humans. (p. 5, l. 5-7) These rodents are useful in understanding the factors involved in weight regulation and in designing and screening for drugs which are involved in weight regulation and that can either enhance or reduce appetite and activity. (p. 5, l. 7-10)

(6) ISSUES ON APPEAL

The issue presented on appeal is whether claims 1, 3-6, and 12-15 should be rejected under 35 U.S.C. § 112, first paragraph

(7) GROUPING OF CLAIMS

The claims do not stand or fall together. Claims 1 and 3-6 are drawn to transgenic rodents. Claim 5 requires that the transgene incorporates the cytomegalovirus promoter and the cytomegalovirus intermediate/early enhancer. Claim 6 specifies a particular genotype, FVB/N-TgN(synd-1).

Claims 10 and 13-15 are drawn to methods for screening of compounds which can alter body weight, by administering the compounds to be screened to an animal as defined by claims 1 and 3-6.

The rejection on appeal is based on the premise that examples showing that different lines of transgenic mice can be made which exhibit the claimed phenotype does not support enablement of claims which encompass transgenic rats made with the same constructs which exhibit the claimed phenotype. As will be discussed in more detail below, this analysis is

believed to be different for claims to the transgenic animals versus claims to the method of use thereof.

(8) ARGUMENTS

(i) The Invention and Data in Support Thereof

Obesity is a well established risk factor for a number of potentially life-threatening diseases such as atherosclerosis, hypertension, diabetes, stroke, pulmonary embolism, and cancer. Furthermore, it complicates numerous chronic conditions such as respiratory diseases, osteoarthritis, osteoporosis, gall bladder disease, and dyslipidemias. More than 50% of all-cause mortality is attributable to obesity-related conditions once the body mass index (BMI) exceeds 30 kg/m^2, as seen in 35 million Americans. The estimated economic impact of obesity and its associated illnesses from medical expenses and loss of income are reported to be in excess of $68 billion/year. (Colditz G. 1992. Am J Clin Nutr. 55:503S-507S). This does not include the greater than $30 billion per year spent on weight loss foods, products, and programs. (Wolf 1994. Pharmacoeconomics. 5:34-37).

A major reason for the long-term failure of established approaches is their basis on misconceptions and a poor understanding of the mechanisms of obesity. Conventional wisdom maintained that obesity is a self-inflicted disease of gluttony. Comprehensive treatment programs, therefore, focused on behavior modifications to reduce caloric intake and increase physical activity using a myriad of systems. These methods have limited efficacy and are associated with recidivism rates exceeding 95%. (NIH Technology Assessment Conference Panel. 1993. Ann Intern Med. 119:764-770). Failure of short-term approaches, together with the recent progress made in elucidating the pathophysiology of obesity, have lead to a reappraisal of

pharmacotherapy as a potential long-term, adjuvant treatment. (National Task Force on Obesity. 1996. JAMA. 276:1907-1915). The premise is that body weight is a physiologically controlled parameter similar to blood pressure and obesity is a chronic disease similar to hypertension. The goal of long-term (perhaps life long) medical therapy would be to facilitate both weight loss and subsequent weight maintenance in conjunction with a healthy diet and exercise. To assess this approach, the long-term efficacy of currently available drugs must be judged against that of non-pharmacological interventions alone. Currently, no single drug regimen emerges as superior in either promoting or sustaining weight loss.

No one knows all of the mechanisms involved in regulation of weight gain, although it is believed that many genetic as well as environmental factors, including diet and exercise, play major, interrelated roles. A number of publications have reported the discovery of genes that have been "knocked out" or overexpressed in transgenic mice, resulting in affected animals becoming incredibly obese, or *vice versa*. Researchers have reported the cloning of at least two distinct genes, Ob which encodes a protein "leptin" believed to cause weight reduction in obese animals, and Db, which is believed to cause weight gain in animals. Other genes which have been reported include the fat, tub, agouti, and melanocortin 4 receptor genes. Leptin, discovered in 1994 by Jeffrey Friedman's team at Rockefeller University, NY, is a 16 kD protein produced by the obesity (ob) gene of mice. Homozygotes with defective ob genes are unable to reproduce, stay warm, or grow normally, and become grossly overweight. The receptor for leptin has now been identified and cloned. Defects in the receptor also result in grossly obese animals. Another molecule which appears to be important in weight control is the appetite-stimulating neurotransmitter referred to as neuropeptide Y or "NPY". NPY levels are elevated in animals with decreased levels of leptin. Genetic studies with knockout NPY and ob/ob animals indicate

that NPY plays a role in, but is not a controlling factor, in obesity. Another line of research has implicated a role in obesity for the melanocortin receptor ("MCR"). Two MCRs, MCR3 and MCR4, are produced in the arcuate nucleus of the hypothalamus, a prime target of leptin action as well as of NPY production. Synthetic peptides mimicking melanocortins which bind to MCR-4 suppress feeding. Animals in which the gene encoding MCR-4 has been knocked out show the opposite behavior, exhibiting high weight gain and high NPY expression. These animals have all therefore been utilized as models for screening of drugs for control of obesity.

Appellants have discovered another animal model to use in screening for compounds affecting weight gain. These animals are genetically engineered using a construct containing (1) a promoter which localizes expression in the hypothalamus, especially in the paraventricular, arcuate, and lateral hypothalamic nuclei, and regulatory sequences required for processing of the transcript, and (2) a nucleic acid molecule encoding a syndecan (page 10, lines 24-28). The promoter that was used in the studies described in the application was the cytomegalovirus (CMV) promoter, a well known commercially available promoter, however, many other neurotropic promoters are known and could have been used. (page 11, lines 1-8). Evidence was provided with the Declaration of Dr. Ofer Reizes signed April 20, 1999 (a copy of which is enclosed) to respond to the examiner's concerns regarding the availability of other promoters.

Cell surface heparan sulfate mediates the activity of several growth factors, extracellular matrix components, proteases and other cellular effectors involved in wound repair. Syndecan-1, a major transmembrane heparan sulfate proteoglycan, is induced transiently on mesenchymal cells during the repair of skin wounds. The syndecan core protein from mouse mammary epithelia was first cloned by Saunders, et al. J Cell Biol. 1989 Apr;108(4):1547-56 (1989). Other syndecans are also known and have now been cloned, including syndecan 2, 3 and 4. These

syndecans constitute the syndecan family. They are characterized by a similar domain structure, highly conserved sequences, and a conserved exon organization in the genes. The molecular sizes of syndecan-1, -2, -3 and -4, are 311 amino acids, 384 amino acids, 201 amino acids, and 202 amino acids. Each protein contains a cluster of similar putative GAG attachment sites distal from the plasma membrane near the N-terminus of the mature protein: one site (or two in syndecan-3) is of the syndecan-type sequence and the other two (or three) sites are of the serglycin-type. Syndecan-1 and -3 contain putative GAG attachment sites that are absent in syndecan-2 and -4. The glycosaminoglycan (GAG) chains on the syndecans are critical to their functions. The functional part of the syndecans are their heparan sulfate chains. The core proteins are thought to be important for localization of the heparan sulfate to the cell surface or the extracellular milleu. Papers were attached to Dr. Reizes's declaration to provide further support on this point. Copies are attached with the declaration.

The examples in the application demonstrate that syndecan-1, under the control of the CMV promoter, can be introduced into transgenic mice using standard techniques, where it will be expressed and "shed" in the hypothalamus and other regions of the brain, and that the animals will be characterized by extreme obesity. The data demonstrate elevated levels of circulating syndecan-1 ectodomain and enormous weight gain after reaching sexual maturity. Transgenic animals in which stop codons have been inserted into the construct so that the syndecan is not expressed do not exhibit the same enormous weight gain. The animals have a relatively normal distribution of fat, are completely healthy and heterozygotes reproduce, and show other indicators associated with obesity in humans. Three different lines of syndecan expressing animals were described in the application, as well as the controls in which stop codons were inserted. These contained insertions at different points in the animals' genomes, and with

different copies (the A insert has a single copy of the syndecan construct inserted; the B insert contains at least two copies of the syndecan construct inserted at one location, distinct from that of A) (page 16, lines 22-25). Regardless of the point of insertion, the same phenotype was observed.

The analysis of the individual animal body weights, sizes and blood levels is described at pages 17-20 and in Table 1 and Figures 4a and b, 5a and 5b, 6,7, 8a and 8b, and 9a and 9b. In response to the examiner's questions about proof that there was preferential expression (or at least some expression) in the hypothalamus, data was also submitted with Dr. Reizes' declaration showing that the syndecan was expressed in the hypothalamic nuclei regulating energy balance. Data was also submitted showing that expression of syndecan-3 is increased by fasting.

(ii) Rejections Under 35 U.S.C. § 112, first pararaph

Claims 1, 3-6, 10 and 12-15 were rejected under 35 U.S.C. §112, first paragraph, on the basis that the application is enabling solely for a transgenic mouse comprising a stably integrated DNA sequence encoding a syndecan operably linked to a promoter, where expression of the DNA sequence results in the mouse developing maturity onset obesity and methods of using these mice. It is this issue which is now on appeal.

a. ***Those skilled in the field of obesity and of transgenic rodents work interchangeably with mice and rats.***

It is the opinion of the inventors, *who are skilled in the field of obesity and of transgenic rodents*, that studies done to make and screen compounds using genetically engineered mice are predictable of the same results in rats. Copies of the articles that demonstrate that results obtained with mice are predictive of results obtained with rats which were submitted to the examiner are enclosed for the convenience of the Board. Also enclosed are abstracts of papers

that are *cumulative* to the papers which were previously submitted, showing that those skilled in the field of obesity and of transgenic rodents, routine make the same genetic changes to both rats and mice, and observe the same phenotypes in response. See for example, studies reported for diabetic mice and rats, mice and rats with high fat induced hyperleptinemia, VMH lesioned mice and rats, and genetic defects resulting in obesity (Frederich, et al., Natl. Med. 1(12):1311-1314 (1995) (mice); Surwit, et al., Diabetes 46(9):1516-1520 (1997) (mice); Suga, et al., Am. J. Physiol. Endocrinol. Metab. 278(4):E677-683 (2000) (rats); Wang, et al., Biochem. Biophys. Res. Commun. 277(1):20-26 (2000) (rats); Wang, et al., Proc. Natl. Acad. Sci. USA 96(18):10373-10378 (1999) (rats)).

1. *An identical methodology is used to generate transgenic mice and rats.*

The literature makes clear that identical methods are utilized in the production of transgenic mice and rats. See DNX transgenic sciences fact sheet, Charles River Laboratories Transgenic Animal Science: Principles and Methods, and Homone Res (1992):37 (suppl 3): 74-87 the Growth Hormone Transgenic Mouse as an Experimental Model for Growth Research: Clinical and pathological Studies, which were submitted to the examiner during prosecution. Because identical methods are used in the generation of transgenic mice and rats, there would be no technical barriers in the use of the mice findings in rats.

2. *Identical phenotypes result from transgenic expression of heterologous genes in the hypothalamus of rats and mice.*

Transgenic mice and rats have been useful in defining a role for GH in development and energy homeostasis. These studies indicate that GH is responsive to physiological stimuli and is released in a pulsatile manner. When human GH is introduced transgenically into mice or rats in an unregulated manner, the results are identical, resulting in acromegaly, obesity and diabetes.

Because transgenic expression of a heterologous gene in the hypothalamus gives rise to identical phenotypes in mice and rats, the data from transgenic mice expressing the syndecan could be easily extrapolated to rats. See Bartke, A., et al., *Effects of growth hormone overexpression and growth hormone resistance on neuroendocrine and reproductive functions in transgenic and knock-out mice.* Proc. Soc. Exp. Biol. Med. 222: 113-123, (1999), and Ideda, A., et al., *Obesity and insulin resistance in human growth hormone transgenic rats.* Endocrinology 139: 3057-3063. (1998).

3. *Use of the CMV promoter leads to expression of heterologous genes in the same hypothalamic nuclei in mice and rats.*

The CMV promoter expresses the syndecan-1 transgene in the mouse hypothalamus, specifically, in the arcuate, paraventricular, supraoptic, suprachiasmatic, dorsomedial and lateral area nuclei. Similarly in the rat, the CMV promoter expresses the kallikrein transgene in identical hypothalamic nuclei when introduced into the third ventricle. Because the same promoter dictates the near identical expression pattern in mice and rats, one would predict the same results in rats as in the transgenic mice. See, Wang, C., et al. *Central delivery of human tissue kallikrein gene reduces blood pressure in hypertensive rats.* BBRC 244: 449-454. (1998).

4. *Identical hypothalamic mechanisms of obesity exist in mice and rats.*

Classical mutations show identical obese phenotypes in mice and rats.

Leptin, a circulating hormone synthesized and secreted by adipocytes, notifies the hypothalamus/brain of the overall level of the body's energy stores. The leptin receptor, a hypothalamically expressed transmembrane signaling protein involved in sensing and responding to circulating levels of leptin, is the *ob* (obese) gene product. Mutations in the leptin receptor in

both mice (*db/db*) and rats (Zucker *fatty*) cause early onset obesity in an identical physiological manner.

Hypothalamic lesions give rise to identical obesity syndromes in mice and rats.

Based on numerous studies involving surgical lesions in mice and rats, the ventromedial, dorsomedial and lateral areas of the hypothalamus are implicated as centers for regulating energy homeostasis. The identical phenotypes are likely due to the identical localization of signaling pathways involved in energy balance in mice and rats. These include the leptin receptor, as well as other neuropeptides and their receptors involved in energy balance, such as neuropeptide Y (NPY) -melanocyte stimulating hormone (MSH), agouti-related protein (Agrp), orexins, melanin concentrating hormone (MCH), and corcicotropin releasing hormone (CRH). Because perturbation of all known hypothalamic signaling cascades in either mice or rats has the same outcome on obesity, results in rats are predictable based on the transgenic mouse data. See, Spiegelman, B.M., et al. *Adipogenesis and obesity: rounding out the big picture.* Cell 87: 377-389 (1996), Flier, J.S., et al. *Obesity and the hypothalamus: novel peptides for new pathways.* Cell 92: 437-440 (1998), and Augustin, K.A., et al. *Rodent mutant models of obesity and their correlations to human obesity.* The Anatomical Record 257: 64-72 (1999).

In summary, the more relevant literature discussed above fully supports that the methods and reagents for making rats using the same methods and reagents as in mice are enabled and predictable, and that the results, i.e., a transgenic animal expressing the syndecan which is characterized by an obese phenotype predictable.

b. Appellants have complied with the legal standard under §112

The standard for making a rejection based on 35 U.S.C. § 112, first paragraph is articulated in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) (see also MPEP § 2164.01 and

2164.04). Initially, the Patent Office must accept the objective truth of statements made in the specification. If such statements are to be called into question, the Patent Office is burdened with providing evidence or convincing argument why those of skill in the art would doubt the statements (*In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971)). Applicants are only required to describe the claimed invention in sufficient detail to enable those of skill in the art to make and use it without the need for undue experimentation. Appellants submit that this has been done.

1. The claims only encompass those animals possessing the claimed phenotype.

The rejection appears to be premised on an allegation that animals not possessing the claimed phenotype fall within the claims. However, this is not a correct interpretation of the claims. Even if one skilled in the art had trouble making a rat with the specified phenotype (and no evidence has been submitted to that end, only observations made with a particular gene encoding a totally unrelated molecule in a completely different physiological situation while appellants have provided numerous examples wherein both rats and mice are used interchangeable as obesity models), it is clear that a rat not having the claimed phenotype would not be within the claim. The claims are limited to those animals expressing a stably integrated DNA encoding a syndecan, where the animal exhibits maturity onset obesity. If the animal expressing a stably integrated DNA encoding a syndecan did not develop maturity onset obesity, it would not be within the scope of the claims. There has been no argument that those skilled in the art could not readily determine if an animal exhibited the characteristics defined by the claims: stable integration of a syndecan-encoding DNA (as demonstrated by the examples) and maturity onset obesity (as also demonstrated by the examples, using measurements that are totally routine and reproducible).

It is unfair and unduly limiting to prohibit appellants from the benefit of their discovery, which is not a mouse but much more than that: that the syndecans can play a major role in obesity when expressed or released into the brain. As the examples and subsequently provided data show, the syndecan levels can be manipulated by genetic engineering *or even diet*; the DNA can be integrated into one or more sites; the DNA can be integrated as a single or multiple copies; it makes no difference. Mice and rats are used as models for obesity - using the same types of surgical interventions, diets and genetic defects to create a system in which compounds can be tested for an effect on weight regulation, and to understand the complex pathways involved in weight control.

2. The lack of evidence with rodents other than mice is not conclusive.

It is well established that the failure to have reduced to practice all embodiments that may fall within the scope of the claims is not proof of non-enablement. In this case the appellants are conducting basic research in a non-profit institution. The production, breeding, analysis and maintenance of transgenic animals is very expensive and requires a lot of room and resources that are simply not available to the appellants. They should not be penalized and others with more resources allowed the benefit of their research for financial reasons.

Even if some of the animals that could be made using constructs encoding syndecans under control of neurotropic promoters did not develop maturity onset obesity, this would not be fatal to the enablement of their claims. This is analogous to the issue in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988), where the Federal Circuit found that the production of claimed monoclonal antibodies in only 2.3% of attempts to make such antibodies was an acceptable amount of experimentation. Significantly, in *Wands* the Federal Circuit was influenced by the fact that in the relevant art, such efforts and rates of success were normal and expected. Applicants submit

that, in the art of transgenic rodents a similar situation exists. It is common, and considered acceptable, that several attempts may be required to produce a transgenic rodent expressing a desired transgene. Such efforts are considered routine and a part of the art.

3. *The burden of proof was shifted to the examiner, who has provided no additional evidence in response to that of the appellants.*

Appellants respectfully submit that, to the extent that enablement was properly questioned by the Patent Office, the evidence now of record clearly indicates that the position taken by the Patent Office is in error, and that the burden of establishing a lack of enablement is clearly shifted back to the Patent Office. In this regard, applicants note that the rejection relies on mere speculation that the claimed transgenic animals would not produce a useful phenotype.

The examiner has provided only two references in support of the proposition "phenotypic alterations resulting from the introduction of a transgene into an animal's genome cannot be predicted, even when the function of the gene is known" (office action mailed July 7, 1999, page 3) and completely ignores the abundance of evidence the appellants have presented: one, it is indeed the function of the molecule, the syndecan, that determines the phenotype, two, the point of insertion and even the number of insertions does not change this phenotype, and three, the study of the genes and roles of compounds in obesity are highly consistent between rats and mice (perhaps in contrast to the two examples the examiner provided, one involving a gene encoding renin and the other involving the introduction of a human HLA gene into rats).

The examiner has taken the position that studies in rats are "less advanced than in the mouse". However, there has been no argument showing that the same promoter, the CMV promoter, and techniques for microinjection that appellants used, work as well in rats as in mice

and appellants have presented evidence that the syndecans in rats are highly homologous to the syndecans in mice.

Not only has the examiner failed to provide any response to the evidence that appellants have provided, other than to reiterate the rejections, but the office action mailed February 1, 2000 appears to be a word processed copy of the rejection. This is clearly improper. The examiner must do more than reiterate the same rejections in view of the appellants response.

(9) SUMMARY

In summary, appellants have provided an abundance of evidence showing that the claims are enabled for rodents expressing a stably integrated syndecan which exhibit maturity onset obesity: demonstrating that animals expressing syndecan from DNA inserts at different points and in different numbers still exhibit the same phenotype; that normal animals can have their syndecan levels manipulated merely by diet (again showing that it is the expressed syndecan, not the point of insertion of the transgene that is critical), that mice and rats are made using the same materials and techniques, without undue experimentation, and that at least in the field of obesity, mice and rats are interchangeable models and predictive of results to be obtained in each species. The examiner has failed to provide any evidence to rebut this proof. Therefore the claims are enabled under 35 U.S.C. §112.

(10) CONCLUSION

For the foregoing reasons, Appellants submit that claims 1, 3-6, 10, and 13-15 are fully enabled by the specification as filed, and should be allowed.

Respectfully submitted,

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CERTIFICATE OF MAILING (37 CFR 1.8)

I hereby certify that this Appeal Brief, along with any paper referred to as being attached or enclosed, is being deposited with the U.S. Postal Service on the date shown below with sufficient postage as first-class in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Date: November 30, 2000

Patrea L. Pabst

APPENDIX: Claims as pending on appeal

1. A transgenic rodent whose genome comprises a stably integrated DNA sequence encoding a syndecanoperably linked to a promoter, wherein expression of the DNA sequence results in the rodent developing maturity onset obesity.

3. The rodent of claim 1 wherein the DNA sequence encodes syndecan -1.

4. The rodent of claim 1 wherein the syndecan is expressed in the areas of the hypothalamus responsible for the regulation of body weight and energy balance.

5. The rodent of claim1 where the promoter is a cytomegalovirus promoter or functional portion thereof, and the CMV intermediate/early enhancer.

6. The rodent of claim 1 having the genotype FVB/N-TgN(synd-1).

10. A method for screening for compounds which can alter body weight comprising:

administering a compound to a transgenic rodent whose genome comprises a stably integrated DNA sequence encoding a syndecan operably linked to a promoter, wherein expression of the DNA sequences results in the rodent developing maturity onset obesity, and

observing whether there is a change in body weight over a period of time.

13. The method of claim 10 wherein the syndecan is expressed in the areas of the hypothalamus responsible for the regulation of body weight and energy balance.

14. The method of claim 10 wherein the promoter is a cytomegalovirus promoter or functional portion thereof, and the CMV intermediate/early enhancer.

15. The method of claim 14 wherein the rodent has the genotype FVB/N-TgN(synd-1).

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